**SUPPORTING STATEMENT**
**FOR**
**Premarket Approval of Medical Devices**
**21 CFR 814**
**OMB No. 0910-0231**

## A. JUSTIFICATION

**The Food And Drug Administration (FDA) has issued a rule (21 CFR Part 814) which prescribes the contents of a premarket approval application (PMA) for a medical device and the criteria the FDA will employ in approving, denying, or withdrawing approval of a PMA. The purpose of this rule is to establish clear and uniform procedures for FDA's review of PMA's for class III (premarket approval) medical devices. FDA has two primary objectives in reviewing PMA applications. First, FDA will facilitate the approval of PMA's for devices that have been shown to be safe and effective and otherwise meet the statutory criteria for approval. Second, FDA will ensure the disapproval of PMA's for devices that have not been shown to be safe and effective and that do not otherwise meet the statutory criteria for approval.**

**Section 515 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360e) sets forth requirements for premarket approval of certain medical devices. Under section 515 of the act, an application must contain several pieces of information. This information should include: Full reports of all information concerning investigations showing whether the device is safe and effective; a statement of components; a full description of the methods used in, and the facilities and controls used for, the manufacture and processing of the device; and labeling specimens. The implementing regulations, contained in part 814, further specify the contents of a PMA for a medical device and the criteria FDA will employ in approving, denying, or withdrawing approval of a PMA. The purpose of these regulations is to establish an efficient and thorough procedure for FDA's review of PMA's for class III (premarket approval) medical devices. The regulations facilitate the approval of PMA's for devices that have been shown to be safe and effective and otherwise meet the statutory criteria for approval. The regulations also ensure the disapproval of PMA's for devices that have not been show to be safe and effective and that do not otherwise meet the statutory criteria for approval.**

**The Food and Drug Modernization Act of 1997 (FDAMA) was enacted on November 21, 1997 to implement revisions to the Federal Food, Drug, and Cosmetic Act. FDAMA streamlines the process of bringing safe and effective drugs, medical devices, and other therapies to the U.S. market. Several provisions of this act affect the PMA process, and are further discussed throughout this supporting statement.**

**On December 30, 1997, the Office of Management and Budget (OMB) conditionally approved reinstatement of this Information Collection for a period of nine months. The collection was given an additional 6 month emergency extension through March 31, 1999. OMB took this action of conditional approval to allow FDA additional time to make changes based on comments received about the PMA program, to comply with the FDA Modernization Act of 1997 (FDAMA), and to complete its own reinvention efforts. OMB has requested that this package be revised to reflect the above conditions when submitting this collection for extension.**

### 1. Circumstances Making the Collection of Information Necessary

**The Food and Drug Administration is requesting approval from the Office of Management and Budget (OMB) for the collection of information in the following regulations: 21 CFR Part 814 (Attachment A).**

**21 CFR 814.15(a)(b)(c) -Reporting**

**Requires most applicants conducting research outside the United States in support of a premarket approval application (PMA) to conduct such research in conformance with the "Declaration of Helsinki" or the laws and regulations of the country where the research is conducted, whichever affords greater protection to the research subjects. Applicants using foreign standards must detail any differences between those standards and the Declaration of Helsinki and explain why the standards offer greater protection to human subjects. For research started before November 19, 1986, FDA must be satisfied that the data is scientifically valid and that the rights, safety, and welfare of the subjects have not been violated.**

**21 CFR 814.20(b) - Reporting**

**Specifies the information required in a PMA and update reports such as the applicant's name and address, a description of the device, its labeling, and its intended uses, and summary of clinical studies.**

**21 CFR 814.37(b)(e) - Reporting**

**Specifies the procedures for amending an incomplete PMA or withdrawing a PMA and resubmitting it.**

**21 CFR 814.39(a) - Reporting**

**Burden for this information collection, included within another proposed rule, has been reported and approved in 0910-0385.**

**21 CFR 814.82(a)(2) - Reporting**

**Requires continued postapproval evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use.**

**21 CFR 814.82(a)(3) & (4) - Disclosure**

**Requires labeling of a device and warnings, hazards, or precautions in the advertising of any restricted device. Also, inclusion of identification codes on the device or its labeling or identification cards.**

**21 CFR 814.82(a)(5) & (6) - Recordkeeping**

**Requires maintenance of records that will enable the applicant to submit to FDA information needed to trace patients if necessary. Maintenance of records for specified periods of time and organization and indexing into identifiable files to ensure the device's safety and effectiveness, to support continued approval of the device.**

**21 CFR 814.82(a)(7) - Reporting**

**Submission to FDA of periodic postapproval reports as required by 814.84 below.**

**21 CFR 814.84(a)(b) - Reporting**

**Requires the holder of an approved PMA to submit periodic reports of new information related to the device or changes in the device that could affect its safety or effectiveness.**

**FDAMA Statutory Provisions**

**Section 201 - Data from Previous Investigations--Statutory burden**

**Allows the submission of data from investigations of earlier versions of a device, in support of safety and effectiveness. Such data is only valid if modifications to earlier versions of the investigational device, whether made during or after the investigation, do not constitute a significant change that would invalidate the relevance of the data. In addition, this section allows for the submission of data or information relating to an approved device that are relevant to the design and intended use of a device for which an application is pending, provided the data are available for use under the FFD&C Act. (i.e. available by right of reference or in the public domain)**

**Section 202 - Special Review for Certain Devices -- Statutory burden**

**FDA will provide special review, which can include expedited processing of a Premarket Approval (PMA) application, for certain devices intended to treat or diagnose life threatening or irreversibly debilitating diseases or**

**conditions. To receive special review, the devices must meet one of the following criteria:**

**1) The device represents a breakthrough technology;**
**2) There are no approved alternatives;**
**3) The use of the device offers significant advantages over existing approved alternatives; or**
**4) Availability is in the best interest of the patients.**

**Section 205 - Meeting on Evidence of Effectiveness for PMA's -- Statutory burden**

**Sponsors planning to submit a Premarket Approval Application (PMA) may submit a written request to FDA for a meeting to determine the type of information (valid scientific evidence) necessary to support the effectiveness of their device.**

**Section 205 - Scope of Review/Collaborative Determinations of Device Data Requirements --**

**• Notices/PMA Supplements for Manufacturing Changes**

**PMA supplements are required for all changes that affect safety or effectiveness, unless such change involves modifications in a manufacturing procedure or method of manufacturing. Manufacturing changes affecting safety or effectiveness may require only a written notice to FDA, which describes the changes in detail and which summarize the information that supports the change. The written notice must also state that the changes were made in accordance with the Quality Systems Regulation (GMPs). The devices subject to manufacturing changes can be distributed 30 days after a notification report is submitted to FDA unless the Agency notifies the submitter that the notice is not adequate.**

**If FDA deems the notice to be inadequate, FDA may request further information or require a PMA supplement. FDA shall review the supplement within 135 days of receipt. The initial 30 day notification review period will be deducted from the 135 day supplement review period if the original notification meets the appropriate content requirements for a PMA supplement.**

**This notification procedure applies only to supplements relating to changes in manufacturing procedures or methods.**

***This section was addressed in a 4/27/98 Federal Register notice which modified 21 CFR Part 814.39 and reported and approved under 0910-0385.***

**•PMA Supplements for Design Changes -- Statutory burden**

**PMA supplements for incremental changes in design affecting safety and effectiveness can be approved based on:**

**non-clinical data that demonstrate the change creates the intended additional capacity, function, or performance of the device; and**
**clinical data included in the original PMA application or any supplement to that application that provides reasonable assurance of safety and effectiveness.**

**However, if needed, FDA may require a sponsor to submit new clinical data to demonstrate safety and effectiveness.**

**Section 207 - Risk Based Classification of Postamendment Class III Devices -- Statutory Burden**

**An applicant who submits a Premarket Notification Submission [510(k)] and receives a Not Substantially**

**Equivalent (NSE) determination, placing the device into a Class III category, can request FDA to classify the product into Class I or II.**

**The request must be in writing and sent within 30 days from the receipt of the NSE determination. In addition, the request must include a description of the device, reasons for the recommended classification (into Class I or II), and information to support the recommendation. Within 60 days from the date the written request is submitted to FDA, the Agency must classify the device by written order.**

**If FDA classifies the device into Class I or II, this device can be used as a predicate device for other 510(k)s.**

**However, if FDA determines that the device will remain in Class III, the device cannot be distributed until the applicant has obtained an approved Premarket Approval (PMA) application or an approved Investigational Device Exemption (IDE).**

**Within 30 days of notifying the applicant of the determination that the device has been classified into Class I or Class II, FDA will announce the final classification in the Federal Register.**

**Section 208 - Classification Panels -- Statutory Burden**

**• Review by the Panel**

**PMA applicants shall have:**

**the same access as FDA to data and information submitted by FDA to a classification panel, except data not available for public disclosure;**
**the opportunity to submit information based on the PMA, through FDA, to the panel; and**
**the same opportunity as FDA to participate in panel meetings.**

**Section 209 - For PMA Collaborative Review Process -- Statutory Burden**

**FDA must, upon the written request of the applicant, meet with that party within 100 days of receipt of the filed PMA application to discuss the review status of the application. With the concurrence of the applicant, a different schedule may be established.**

**Prior to this meeting, FDA must inform the applicant in writing of any identified deficiencies and what information is required to correct those deficiencies. FDA must also promptly notify the applicant if FDA identifies additional deficiencies or of any additional information required to complete Agency review.**

**Summary**

**The Medical Device Amendments of 1976 require all medical devices to be classified into one of three regulatory categories. Class I devices are subject to only general regulatory controls which are applicable to all products. Class II devices require performance standard and special controls to ensure their safety and effectiveness. Class III devices, such as implanted, life-sustaining devices or devices which otherwise present a potentially unreasonable risk of illness or injury, require premarket approval.**

**The regulation in 21 CFR Part 814 implement section 515 of the Federal Food, Drug, and Cosmetic Act (Attachment B) by providing procedures for the premarket approval of medical devices intended for human use. Any class III device, unless exempt under section 520(g) of the Act, in commercial distribution before May 28, 1976, or a post-Amendments device which is substantially equivalent to such a device, does not need premarket approval until 30 months after FDA places the device into class III or until 90 days after FDA calls for such premarket approval applications, whichever is later. Section 515 of the Act also requires manufacturers of post-Amendments class III devices that are not substantially equivalent to a pre-Amendments device to submit data to**

**FDA that provide reasonable assurance of the device's safety and effectiveness before those devices enter commercial distribution in the United States.**

**FDAMA was enacted to implement revisions to the Federal Food, Drug, and Cosmetic Act and streamline the process of bringing safe and effective drugs, medical devices, and other therapies to the U.S. marketplace**

**2. Purpose and Use of the Information**

**This PMA Regulation establishes procedures that FDA utilizes in approving, denying, or withdrawing approval of any PMA. The PMA regulation provides specific, clear, and flexible instructions to applicants so they know what information is required in a PMA. FDA reviews applications according to 21 CFR 814.42 (which describes grounds for accepting or refusing to file a PMA). If this information is not collected, FDA cannot ensure that devices are safe and effective.**

**3. Use of Information Technology and Burden Reduction**

**FDA believes that the PMA regulation is flexible enough to allow for improved technology for data collection.**

**Electronic Signatures Regulation (eSig) [21 CFR Part 11], which became effective August 20, 1997, permits FDA to accept documents or portions of regulatory applications in electronic format in lieu of paper.**

**FDA is using information technology to reduce the information burden to respondents of information queries. Presently, respondents to FDA information collections may use computer wordprocessing, electronic forms, spreadsheet, and database software to collect and format information for submission to FDA. FDA has reduced the burden of responding to regulatory statute through the use of these electronic applications, their Fax-On-Demand fax back system, their Electronic Docket, and the Internet.**

**FDA has attempted to maximize current technology to reduce burden for respondents of its data by the methods mentioned above. FDA will continue to pursue methods of applying technology to reduce burden to the respondents of its information collections.**

**4. Efforts to Identify Duplication and Use of Similar Information**

**This information cannot be obtained from any source other than the manufacturer, therefore this effort is not duplicated elsewhere. Holders of approved PMAs who had to comply with the new drug requirements before the rule was promulgated are no longer required to comply with those regulations but rather are to comply with 21 CFR Part 814.**

**No similar data are available to or collected by FDA because each PMA is product and manufacturer specific. Most information in a PMA is unique and is presented to support claims of safety and effectiveness for that particular purpose.**

**5. Impact on Small Businesses or Other Small Entities**

**The FDA exercises caution and discretion when implementing additional recordkeeping requirements to industry. FDA recognizes that submission of this data may be a hardship for small businesses, but every business, regardless of its size, should provide reasonable assurance of their device's safety and effectiveness before commercial marketing. In the last several years, on average, 47 percent of the PMAs received by FDA were from manufacturers who had 500 or more employees; 34 percent of PMAs were from manufacturers with under 100 employees.**

**The FDA has established a Division of Small Manufacturers Assistance (DSMA), as required by Federal law, to provide technical and non-financial assistance to manufacturers. The office uses a comprehensive program of on-site inspections (when requested by a firm), seminars, educational conferences, informational materials, fax back**

**system, and toll-free telephone number which any manufacturer can use. This staff and the Office of Device Evaluation are available to answer manufacturers' questions at any time.**

**In addition, the FDA/CDRH is reengineering the PMA process. The PMA Reengineering team's goal is to develop an IDE/PMA process that focuses resources on high-impact and high-risk products and produces smart, fast, and fair review decisions. In that regard, the PMA Team developed a seamless model IDE/PMA process and pilot programs to provide efficient, timely, and fair PMA decisions. Using extensive input from all stakeholder groups, the new model creates early meetings with industry to identify data needs (the PMA "shell"), and resolves issues much earlier through a "modular review" process. By targeting decisions in 180 review days, the managed process eliminates unnecessary re-review of data and focuses resources on high-impact and high-risk devices by providing different review tracks: expedited, standard and streamlined.**

**A system, developed as a joint project between the team and HIMA, was devised to provide more predictability and consistency in determining when a supplement or report is needed for modification of a PMA device.**

**For the future, the PMA team has assembled a list of potential process improvements and is pursuing the highest priorities. There are no other additional major processes, but additional lower priority issues should eventually be addressed. One example would be the master files, which could be improved, and, if additional resources are made available to the IDE/PMA program, enhanced IDE/PMA project management could improve review efficiency.**

**Reengineering of the IDE/PMA process to benefit Small Businesses will require cooperation between FDA and its respondents, new procedures, and training. It will complement changes required by FDAMA.**

**6. Consequences Collecting the Information Less Frequently**

**Manufacturers determine when a product will be submitted for premarket approval. FDA determines subsequent reporting requirements and their frequency based on the necessity for manufacturers to provide reasonable assurance of their device's continued safety and effectiveness. If this information were not collected, FDA could not ensure that devices were safe and effective.**

**7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5**

**The 5 CFR 1320.5 requirements are met with the exception which requires that not more than 1 original and 2 copies be submitted. The requirement at 21 CFR 814.20(b)(2) to submit 6 copies of the PMA is reasonable and results in efficient and expeditious PMA reviews. Additional copies may be requested to review and discuss information and data in a PMA, so that a copy of the entire PMA is made available to each member of the pertinent advisory committee (six to eight members). Certain information is also made available to the consumer representative and to the industry representative of the advisory committee. FDA maintains the original PMA in the PMA Document Mail Center in its Center for Devices and Radiological Health (CDRH). Additional copies are used for concurrent review by CDRH personnel, such as the ODE Division, Biometrics, GMP manufacturing inspection staff, and Bioresearch Monitoring. The final copy is retained for team review by other statisticians, physicians, and scientists.**

**Fewer copies may be submitted if the omissions is justified under 814.20(d). Few manufacturers have objected to the request for 6 copies (or more if needed) because the review process is substantially expedited to their advantage. If FDA were required to construct review copies for concurrent review by FDA personnel or advisory committee review, substantial delays would be anticipated due to lack of equipment and personnel to perform the copying and collation of the documents.**

**8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency**

**Notice was published in the Federal Register on October 6, 1998 in Docket No. 98N-0721 soliciting comments on this information collection prior to its submission to the Office of Management and Budget (OMB) as required by 5 CFR 1320.8(d) (see Attachment C). No comments were received.**

**Comments Received During Federal Register 60 Day Review Period**

**This information collection was the subject of a notice requesting comments from the public. Prior to OMB's conditional approval on December 30, 1997, comments were received by F. Mac McKeen, Regulatory Affairs Associate with Cardiac Pacemakers, Inc. (CPI), Guidant Corporation, St. Paul Minnesota (Attachment D) during the 60 day comment period which ended March 7, 1997. On CPI/Guidant's behalf, Mr. F. Mac McKeen, made several observations about this collection (OMB Information Collection 0910 –0231) and PMA regulation 21 CFR 814. CPI/Guidant's comments addressed the areas of 1) necessity of collection of information for proper performance of FDA's functions; 2) ways to enhance the quality, utility, and clarity of the information to be collected; 3) single reporting system; and 4) ways to minimize the burden of the collection on respondents.**

**CPI/Guidant Comments**

**Regarding the area of information necessity and GMP supporting documentation, CPI/Guidant has questioned the usefulness of this information and offered an alternative "Master File" approach to this collection, especially in the areas of manufacturing and sterilization. To enhance the quality, utility, and clarity of the information to be collected, CPI/Guidant indicated that a final report review is an ineffective way to provide early feedback to companies, and suggested a "Pre-PMA" program be established. Real-time reviews were also offered as a way to answer reviewers questions immediately, and allow FDA the opportunity to schedule specific-skilled employees in an effort to more efficiently balance FDA's workload.**

**CPI/Guidant noted the post-approval requirements section (21 CFR 814.80) overlaps the Post Market Surveillance requirements in the Safe Medical Device Act, Device Tracking regulation, and the Medical Device Reporting regulation. CPI/Guidant documented this overlap in a table attached to their comment correspondence. Finally, CPI/Guidant suggested ideas to minimize the burden to respondents, specifically, that electronically formatted submissions greatly enhance both industry and FDA reviewers and make their work much easier. CPI/Guidant requested that FDA create a guidance document with standards for electronic submissions, and that this document is vital for this collection. In addition, CPI/Guidant noted that FDA should adopt a true "electronic submission" program that involves the submission of this information collection's requirements on electronic media, such as CD-ROM. This practice alone would save paper, minimize the handling of documents, and also serve to meet the objectives of the Paperwork Reduction Act. CPI/Guidant's comments are stated in Attachment D at the end of this document.**

**FDA Response to CPI/Guidant Comments**

**The comments provided to FDA/CDRH by Mr. McKeen on behalf of CPI/Guidant Corporation have been addressed below by CDRH's Office of Device Evaluation's (ODE) PMA program office as a part of FDA's on going reengineering effort and implementation of the FDA Modernization Act of 1997 (FDAMA).**

**ODE has stated that the Office of Compliance (OC) is currently writing new guidance based on the quality system regulation which should address these points for future original PMA submissions. In addition, to reduce burden on the applicant, an FDA/Industry working group is reviewing PMA supplement requirements which would make certain manufacturing changes reportable either in an annual report or to a file kept at the applicants site.**

**The FDA/CDRH's Office of Device Evaluation (ODE) has been accepting presubmission PMAs for more than a year on an informal basis. A more formal mechanism (policy and tracking system) is planned due to the FDAMA requirements.**

**CPI/Guidant has suggested an interactive, real-time type of review for larger PMA submissions. The Food and Drug Administration Modernization Act of 1997 requires that FDA facilitate a collaborative review process for PMAs, and implementation of this provision should allow for a more interactive type of FDA review. Additional policy is currently being written to address this new provision in the law.**

**The Food and Drug Administration Modernization Act of 1997 (FDAMA) may have addressed the issue of a single performance data reporting system for postapproval requirements through its modified postapproval requirements under section 522 of the act. There is no longer a requirement for postmarket surveillance for certain devices, and this should reduce overlap in postapproval requirements.**

**The Office of Device Evaluation (ODE) is currently developing formal guidelines about electronic submissions. Until the guidelines are finalized, CDRH is requesting industry to give prior notification of their desire to submit an application in electronic form, which will assure that the reviewer has the necessary hardware and software to review the electronic application and facilitate the review process. FDA/CDRH has been accepting electronic submissions for over a year.**

**CDRH's Reengineering Task Force periodically takes a critical look at current CDRH procedures to be sure that they are in the best interest of the public health. Presently, the Task Force is assisting CDRH in the development of a streamlined IDE/PMA process which will contribute towards the completion of IDE/PMA reviews more efficiently. CPI/Guidant's comments and other input from industry and within FDA are being reviewed for incorporation in the new IDE/PMA process model.**

**The Reengineering Task Force, in conjunction with the Office of Device Evaluation PMA program, is currently reviewing all comments received regarding the IDE/PMA review process. At the present time, it is premature to decide how these comments, including the ones from CPI/Guidant, will be implemented in the IDE/PMA review process.**

**<u>Compliance with the FDA Modernization Act of 1997</u>**

**The Food and Drug Modernization Act of 1997 (FDAMA) enacted on November 21, 1997 to implement revisions to the Federal Food, Drug, and Cosmetic Act, streamlines the process of bringing safe and effective drugs, medical devices, and other therapies to the U.S. market. Several provisions of this act affect the PMA process, and are discussed below. FDA has implemented or will implement all provisions of FDAMA which affect the PMA process.**

**Section 201, Data from Previous Investigations, allows submission of data from investigations of earlier versions of a device, in support of safety and effectiveness. The data is valid if modifications to earlier versions of the investigational device, whether made during or after the investigation, do not constitute a significant change that would invalidate the relevance of the data. This section also allows for the submission of data or information relating to an approved device that are relevant to the design and intended use of a device for which an application is pending, provided the data are available for use under the FFD&C Act. (i.e. available by right of reference or in the public domain).**

**Section 202, Special Review for Certain Devices, states that FDA will provide special review, which can include expedited processing of a Premarket Approval (PMA) application, for certain devices intended to treat or diagnose life threatening or irreversibly debilitating diseases or conditions.**

**Section 205, Meeting on Evidence of Effectiveness for PMA's, will allow sponsors planning to submit a Premarket Approval Application (PMA) to submit a written request to FDA for a meeting to determine the type of information (valid scientific evidence) necessary to support the effectiveness of their device. FDA must meet with the requester and communicate in writing the Agency's determination of the type of data that will be necessary to demonstrate effectiveness within 30 days after the meeting.**

**Although the meeting under Section 205 (intended to focus on the type of valid scientific evidence that will be necessary), and the meeting under Section 201 (intended to focus on the actual protocol) are listed separately, FDA believes the purposes of the meetings can usually most effectively be accomplished in a single meeting. However, some sponsors may request and benefit from two separate meetings.**

**Section 205, Scope of Review/Collaborative Determinations of Device Data Requirements, discusses Labeling**

**Claims for PMA's, PMA Supplements for Manufacturing Changes, PMA Supplements for Design Changes, and Postmarket Controls to Reduce Data Requirements.**

**Labeling Claims for PMA's says that FDA is to rely on the conditions of use submitted as proposed labeling in the PMA application, so long as the proposed labeling is neither false nor misleading. In determining whether or not such labeling is false or misleading, FDA shall fairly evaluate all material facts pertinent to the proposed labeling. This provision is consistent with the way FDA has always reviewed PMAs.**

**Notices/PMA Supplements for Manufacturing Changes state that PMA supplements are required for all changes that affect safety or effectiveness, unless such change involves modifications in a manufacturing procedure or method of manufacturing. Manufacturing changes affecting safety or effectiveness may require only a written notice to FDA, which describes the changes in detail and which summarize the information that supports the change and states that the changes were made in accordance with the Quality Systems Regulation (GMPs). The devices subject to manufacturing changes can be distributed 30 days after a notification report is submitted to FDA unless the Agency notifies the submitter that the notice is not adequate. Inadequate notices may require further information or a PMA supplement be submitted to FDA. FDA shall review the supplement within 135 days of receipt. The initial 30 day notification review period will be deducted from the 135 day supplement review period if the original notification meets the appropriate content requirements for a PMA supplement. This notification procedure applies only to supplements relating to changes in manufacturing procedures or methods.**

**PMA Supplements for Design Changes allows for approval of incremental changes in design affecting safety and effectiveness based on non-clinical data that demonstrate the change creates the intended additional capacity, function, or performance of the device; and clinical data included in the original PMA application or any supplement to that application that provides reasonable assurance of safety and effectiveness. If needed, FDA may require a sponsor to submit new clinical data to demonstrate safety and effectiveness.**

**Postmarket Controls to Reduce Data Requirements states that, while making a determination regarding the approval of a PMA application, FDA must consider if postmarket controls can be relied on to reduce the extent of data pertaining to effectiveness that otherwise would be required to support approval.**

**Section 207 - Risk Based Classification of Postamendment Class III Devices, allows an applicant who submits a Premarket Notification Submission [510(k)] and receives a Not Substantially Equivalent (NSE) determination, placing the device into a Class III category, to request FDA to classify the product into Class I or II. The request must be in writing and sent within 30 days from the receipt of the NSE determination. Within 60 days from the date the written request is submitted to FDA, the Agency must classify the device by written order.**

**If FDA classifies the device into Class I or II, this device can be used as a predicate device for other 510(k)s. However, if FDA determines that the device will remain in Class III, the device cannot be distributed until the applicant has obtained an approved Premarket Approval (PMA) application or an approved Investigational Device Exemption (IDE).**

**Within 30 days of notifying the applicant of the determination that the device has been classified into Class I or Class II, FDA will announce the final classification in the Federal Register.**

**Section 208 - Classification Panels, allow for scheduling of meetings, review by the panel, and final decision.**

**Scheduling of Meetings is done so that the FDA time frames for approval of PMA and 510(k) applications can be met.**

**Review by the Panel allows PMA applicants to have the same access as FDA to data and information submitted by FDA to a classification panel, except data not available for public disclosure; the opportunity to submit information based on the PMA, through FDA, to the panel; and the same opportunity as FDA to participate in panel meetings.**

**If final decisions to approve or disapprove an application differ from the panel recommendation, FDA shall provide**

**reasons for this determination to the applicant in writing.**

**Section 209 - For PMA Collaborative Review Process states that FDA must, upon the written request of the applicant, meet with that party within 100 days of receipt of the filed PMA application to discuss the review status of the application. With the concurrence of the applicant, a different schedule may be established. Prior to this meeting, FDA must inform the applicant in writing of any identified deficiencies and what information is required to correct those deficiencies. FDA must also promptly notify the applicant if FDA identifies additional deficiencies or of any additional information required to complete Agency review.**

**Section 216 - Use of Data says FDA can now use certain information, contained in approved PMA applications, six years after the application has been approved to approve another PMA application; determine whether a Product Development Protocol (PDP) has been completed; establish a performance standard or a special control; or classify or reclassify another device.**

**Information available for the Agency to use would include clinical and non-clinical tests or studies in the application that were used to demonstrate safety and effectiveness. However, it would exclude trade secret information such as manufacturing methods or device composition.**

**Section 216 - Product Development Protocol (PDP) states that FDA is no longer required to refer all PDP's to panel. The Agency now has discretion to refer a proposed protocol to an advisory panel for recommendation regarding approval before making a determination. However, FDA is required to refer the proposed protocol to the panel if requested by the submitter, unless the protocol and accompanying data substantially duplicate information that has been reviewed by the panel previously.**

**Section 217 - Clarification of the Number of Required Clinical Investigations for Approval allows FDA to rely on one or more clinical investigations to conclude that a device that is the subject of a PMA application is effective or to establish a device performance standard.**

**Section 403 - Approval of Supplemental Applications establishes standards for prompt review, guidance to industry, a designated individual, and collaboration with outside organizations.**

**Under "Standards for Prompt Review", the FDA will publish, in the Federal Register (FR), standards the Agency will use to assure prompt review of a PMA supplement.**

**"Guidance to Industry" states that FDA will publish final guidance to clarify the requirements for, and facilitate the submission of, data to support a PMA supplement. This guidance will clarify when published information can be used as the basis of approval; specify data requirements that will avoid duplication of previously submitted data used to support the original PMA application; and identify types of supplements that are eligible for priority review.**

**A "Designated Individual" is a person designated from the Center for Devices and Radiological Health to encourage prompt review of supplements by FDA and to work with sponsors to facilitate both the development and submission of data necessary to support a PMA supplement.**

**"Collaboration with Outside Organizations" discusses how FDA will implement programs and policies to foster collaboration with outside organizations, including the National Institutes of Health, medical and scientific associations, and others for purposes of identifying studies that may support PMA supplements. This also encourages sponsors to make supplemental applications or conduct further research to support supplements.**

**<u>Completion of FDA's Reengineering Efforts</u>**

**During the past several years, FDA/CDRH has reengineered several regulatory processes. As this is an ongoing effort, total completion of the entire reengineering tasks for FDA/CDRH is several years away. However, PMA process reengineering efforts have contributed, and will continue to contribute towards reduction of burden to respondents and a more efficient and streamlined program. All reengineering efforts complement changes**

**required by FDAMA.**

**Accomplishments: The goal of the PMA Reengineering Team is to develop an IDE/PMA process that focuses resources on high-impact and high-risk products and produces smart, fast, and fair review decisions. The following are examples of how reengineering efforts at FDA/CDRH have contributed towards meeting the goal of the team.**

**In the past year, the team has developed a seamless model IDE/PMA process and pilot programs to provide efficient, timely, and fair PMA decisions. By using extensive input from all stakeholder groups, the new model creates early meetings with industry to identify data needs (the PMA "shell"), and resolves issues much earlier through a "modular review" process. By targeting decisions in 180 review days, the managed process eliminates unnecessary re-review of data and focuses resources on high-impact and high-risk devices by providing different review tracks: expedited, standard and streamlined.**

**A pilot program has begun in DCLD for a streamlined-review track for PMAs of devices that are well understood and have established criteria.**

**A system, developed as a joint project between the team and the Health Industry Manufacturers Association (HIMA), was devised to provide more predictability and consistency in determining when a supplement or report is needed for modification of a PMA device.**

**By working with the Grassroots Premarket Subcommittee and the GMP Reengineering Team, a system was introduced to ensure the best use of inspection resources for PMA products.**

**Procedures for streamlining PMA sign-off and delegation options were expanded to maximize efficiency.**

**As a project management tool, procedures were created to improve the efficiency of development & use of the PMA Summary of Safety and Effectiveness Data.**

**A pilot continues in the Dental Branch to develop tools for PMA project managers as additional project management options are developed. An IDE/PMA "Toolbox" web page is being developed to provide all stakeholders with ready access to relevant guidelines, procedures, and examples that facilitate the IDE/PMA process.**

**Two pilots were initiated for product labeling across ODE. One established Standard Operating Procedures (SOPs) for review and closure on final draft labeling, including an interactive meeting with the sponsor. The other eliminated re-review of final printed labeling where it is either the same as the approved draft labeling or contains only minor changes.**

**The team implemented shared access to PMA inspection database information between FDA/CDRH's Office of Device Evaluation (ODE) and Office of Compliance (OC). This access speeds communications and allows identification and earlier resolution of inspection issues.**

**Current Status: Implementation of the IDE/PMA review model development process is underway. Draft SOPs for modular review are being circulated for comment and industry input is being evaluated. Assessment of the Dental Branch Project Management Milestones Pilot was due March 31, 1998. The IDE/PMA "Toolbox" will be on hold until the project can be merged with the Device Advice project (an interactive Web-Site being piloted by OHIP that consolidates medical device information for both Agency and industry). DCLD sent letters to industry announcing availability of the pilot for streamlined in-vitro diagnostic PMA review. The PMA inspection project with the Grassroots Premarket Subcommittee will be pursued with the GMP Team, ODE, and OC to refine the proposal and obtain comment on the draft.**

**FDA/HIMA's PMA modification flowchart is ready for Agency and public comment. Redelegation of sign-off authority for some PMA products to Division directors has been approved effective March 18, 1998. Final draft**

**plans for Summaries of Safety & Effectiveness Data were due April 1998. Results of the pilot studies for the review of final draft labeling and re-review of final printed labeling were assessed in April 1998. The PMA team is also closely coordinating its reengineering efforts with the initiatives required under the FDA Modernization Act (FDAMA).**

**Future Initiatives: The PMA team assembled a list of potential process improvements and is pursuing the highest priorities. There are no other additional major processes, but additional lower priority issues will eventually be addressed. One example would be the master files, which could be improved. Also, if additional resources are made available to the IDE/PMA program, enhanced IDE/PMA project management could improve review efficiency.**

**Reengineering of the IDE/PMA process will require considerable buy-in by the medical device community, new procedures, and training. It will complement changes required by FDAMA.**

**Consultations**

**The Center for Devices and Radiological Health, primarily through its Division of Small Manufacturers Assistance, regularly meets, corresponds, and talks with the industry either informally, such as through its toll-free number or through the many training sessions it holds throughout the country. FDA also communicates with affected persons regularly through organizations such as the Health Industry Manufacturers Association (HIMA), a trade organization representing manufacturers and the Food and Drug Law Institute, and educational organization consisting primarily of attorneys practicing in the Food and Drug law area. Problems raised in these communications have been addressed by the built-in flexibility provided by the PMA regulation. CDRH has issued general guidance in its "Premarket Approval Manual" (HHS Publication FDA 93-4214) (Attachment C) and also in guidance for specific products such as its "Guidance for Class III Contact Lenses.".**

**The following individuals were consulted regarding the burden associated with this information collection.**

**Nancy Singer, Esq., Health Industry Manufacturers Association (HIMA), 202-434-7222. January, 1993. Regulation generally acceptable. FDA needs to apply additional resources to PMA review. Suggested changes to PMA supplement portion of the regulation. Changes are being drafted.**

**Jonathan Kahan, Esq., Hogan and Hartson, private attorney representing medical device industry. 202-637-5794, Medical Design and Manufacturing Conference, January, 1993. Agency needs to be more flexible in application of regulation. Need more consistency and predictability among reviewers.**

**Mark A. Heller, Esq., Patton, Boggs, and Blow, private attorney representing medical device industry, 202-457-6018. FDA needs to draft and implement additional guidelines to clarify regulation. Guidelines are being drafted.**

**James Blanchard and Dee Simon, Health Industry Manufacturers Association (HIMA), 202-434-7222. August, 1996. HIMA is researching data in their files regarding the burden cost of producing a PMA package for FDA.**

**9. Explanation of Any Payment or Gift to Respondents**

**There is no provision for any payment or gift to respondents.**

**10. Assurance of Confidentiality Provided to Respondent**

**Confidentiality of data and disclosure regarding the existence of a PMA are governed by 21 CFR 814.9, the Freedom of Information Act (FOIA) (5 U.S.C. 552), and sections 301(j), and 520© and (h) of the FD&C Act (21 U.S.C. 331(j), 360© and (h)). Under FOIA, the public has broad access to government documents.**

**However, FOIA provides certain exemptions from mandatory public disclosure of government records (5 U.S.C. 552(b) (1-9). One such provision, 5 U.S.C. 552(b) (4), exempts "trade secrets and commercial or financial**

**information that is privileged or confidential" from the requirement of public disclosure. Section 520© of the FD&C Act prohibits FDA from disclosing any information exempted from public disclosure under 5 U.S.C. 552(b) (4). Part 20 of FDA's regulations, 21 CFR Part 20, sets forth FDA's general policy concerning public availability of FDA records. Under section 520(h) of the Act, FDA is required to make publicly available a detailed summary of the safety and effectiveness information contained in a PMA that is the basis for an order approving, denying approval of, or withdrawing approval of a PMA.**

**11. Justification for Sensitive Questions**

**The premarket approval application does not contain questions pertaining to sexual behavior, attitude, religious beliefs, or any other matters that are commonly considered private or sensitive in nature.**

**12. Estimates of Burden Hours Including Annualized Hourly Costs**

**Respondents to this information collection are persons filing an application with the Secretary of Health and Human Services for approval of a Class III medical device. Part 814 defines a person as any individual, partnership, corporation, association, scientific or academic establishment, government agency or organizational unit, or other legal entity. These respondents include manufacturers of commercial medical devices in distribution prior to May 28, 1976 (the enactment date of the Medical Device Amendments).**

**FDA estimates the burden of this collection of information as follows:**

| Estimated Annual Reporting Burden | | | | | |
|---|---|---|---|---|---|
| **21 CFR Section** | **No. of Respondents** | **Annual Frequency per Response** | **Total Annual Responses** | **Hours per Response** | **Total Hours** |
| 814.15, 814.20, and 814.37 | 52 | 1 | 52 | 837.28 | 43,539 |
| 814.82 | 37 | 1 | 37 | 134.68 | 4,983 |
| 814.84 | 37 | 1 | 37 | 10 | 370 |
| Section 201 (FDAMA) | 52 | 1 | 52 | 10 | 520 |
| Section 202 (FDAMA) | 15 | 1 | 15 | 10 | 150 |
| Section 205 (FDAMA) | 25 | 1 | 25 | 50 | 1250 |
| Section 207 (FDAMA) | 10 | 1 | 10 | 50 | 500 |
| Section 208 (FDAMA) | 26 | 1 | 26 | 30 | 780 |
| Section 209 (FDAMA) | 52 | 1 | 52 | 40 | 2080 |
| TOTALS | | | | | 54,172 |

**There are no capital costs or operating and maintenance costs associated with this collection of information.**

**Table 2.--Estimated Annual Recordkeeping Burden**

| 21 CFR Section | No. of Recordkeepers | Annual Frequency of Recordkeeping | Total Annual Records | Hours per Recordkeeper | Total Hours |
|---|---|---|---|---|---|
| 814.82 (a) (5) & (a) (6) | 814 | 1 | 814 | 16.7 | 13,594 |
| Totals: | | | | | 13,594 |

**There are no capital costs or operating and maintenance costs associated with this collection of information.**

**FDA estimates that the cost to device manufacturers to comply with the requirements for premarket approval of medical**

**devices is approximately $34.95 million per year. The industry-wide cost estimate for PMA's is based on an FDA actual average fiscal year annual rate of receipt of 52 PMA original applications and 493 PMA supplements, using fiscal years 1991 through 1997 data.**

**The cost data for PMAs is based on data provided by manufacturers in 1985 by device type and cost element. The specific cost elements for which FDA has data are as follows:**

**a. Clinical investigations: 67% of total cost estimate**

**b. Submitting additional data or information to FDA during a PMA review: 12%**

**c. Additional device development cost (e.g., testing): 10%**

**d. PMA and PMA supplement preparation and submissions, and development of manufacturing and controls data: 11%.**

**A weighted-average calculation in 1985 produced a total cost of $280,000 for a PMA application. These cost estimates are considered to be solely attributable to PMA requirements. FDA does not have more recent data on the cost to manufacturers of collecting, analyzing, and preparing the data needed for a PMA submission. FDA has adjusted the 1985 estimate for inflation (using an average of 7.5 percent per year for the health care sector) and multiplied it by 52 (the average number of PMAs submitted annually) to yield an annual cost attributable to PMAs of $32,323,200 ($280,000 x index of 2.22 x 52).**

## Paperwork Burden Estimate

**The estimated total annual reporting and recordkeeping burden for this information collection is 67,766hours.**

## REPORTING/DISCLOSURE

**The reporting burden can be broken out by certain sections of the PMA regulation.**

**Section 814.15 - Research Conducted Outside U.S.**
**Section 814.20 - Applications:**
**Section 814.37 - PMA Amendments and Resubmitted PMAs:**

**The majority of the burden - 43,539 burden hours - is due to the above three requirements. Included in these three requirements are the conduct of laboratory and clinical trials as well as the analysis, review, and physical preparation of the PMA application. FDA estimates that 52 respondents will be affected by these requirements based on actual average FDA receipt of new PMA applications in years 1991 through 1997. FDA's estimate of the hours per response (837.28) was derived through FDA's experience and consultation with industry and trade associations. Included in these three requirements are the conduct of laboratory and clinical trails as well as the analysis, review, and physical preparation of the PMA application. FDA estimates based on the 1985 study that these requirements account for the bulk of the burden identified by manufacturers.**

**21 CFR 814.39 - PMA Supplements: 32,612 burden hours**

**Clearance for this information collection, included within a proposed rule, has already been sought by FDA in an earlier document (63 FR 20558).**

**21 CFR 814.82 - Postapproval Requirements: 4,983 burden hours.**

**Postapproval requirements concern approved PMAs which were not reclassified and require an annual report. In the last decade (1988-1997), the range of PMAs which fit this category averaged approximately 37 per year (70 percent of the 52 annual submissions). Most approved PMAs have been subject to some restriction. Approximately half of the average**

**submitted PMAs (26) require associated postapproval information (i.e., clinical trials or additional pre-clinical information) that is labor-intensive to compile and complete, and the other PMAs require minimal information. Based on its experience and on consultation with industry, FDA estimates that preparation of reports and information required by this section require 4,983 hours (134.68 hours per respondent).**

**21 CFR 814.84 - Reports: 370 burden hours.**

**Postapproval requirements described in 21 CFR 814.82 (above) require a periodic report. FDA has determined respondents meeting the criteria of 21 CFR 814.84 will submit reports on an annual basis. As stated previously, the range of PMAs fitting this category averaged approximately 37 per year. These reports have minimal information requirements. FDA estimates that respondents will construct their report and meet their requirements in approximately 10 hours. This estimate is based on FDA's experience and on consultation with industry. FDA estimates that the periodic reporting required by this section take 370 hours.**

**utory Burden: The total hours for statutory burden is 5,280.**

**RECORDKEEPING**

**The recordkeeping burden in this section involves the maintenance of records to trace patients and the organization and indexing of records into identifiable files to ensure the device's continued safety and effectiveness. These records would be required only of those manufacturers who have an approved PMA and who had original clinical research in support of that PMA. For a typical year's submissions, 70 percent of the PMAs are eventually approved and 75 percent of those have original clinical trial data. Therefore, approximately 37 PMAs a year (52 annual submissions times 70 percent) would be subject to these requirements. Also, because the requirements apply to all active PMAs, all holders of active PMA applications must maintain these records. PMAs have been required since 1976, so there are 814 active PMAs that could be subject to these requirements (22 years x 37 per year). Each study has approximately 200 subjects, and, at an average of 5 minutes per subject, there is a total burden per study of 1,000 minutes, or 16.7 hours. The aggregate burden for all 814 holders of approved original PMAs, therefore, is 13,594 hours (814 approved PMAs with clinical data x 16.7 hours per PMA).**

**The applicant determines which records should be maintained during product development to document and/or substantiate the device's safety and effectiveness. Records required by the Current Good Manufacturing Practices for medical devices regulation (21 CFR 820) may be relevant to a PMA review and may be submitted as part of an application. In individual instances, records may be required as conditions to approval to ensure the device's continuing safety and effectiveness.**

**13. Estimate of Other Total Annual Cost Burden to Respondents or Recordkeepers**

**There are no additional costs associated with this information collection.**

**14. Annualized Cost to the Federal Government**

**FDA estimates that approximately 155 staff-years are devoted to the activity annually, at a cost of $12.9 million. The average time modules for the activity are 1.2 staff-years for a PMA review and 0.1 staff-years for a supplemental PMA. The cost estimate includes FDA staff effort and advisory panel costs for those PMA's requiring panel review under the law, as changed by the Safe Medical Devices Act of 1990.**

| FTEs | Cost/FTE | Total Cost |
|---|---|---|
| 155 | $93,500 | $14,492,500 |

**15. Explanation for Program Changes or Adjustments**

**Explanation of Burden Change**

**There has been a reduction of respondent burden hours since this information collection's OMB approval on December 30, 1997. The total respondent burden hours have decreased from 104,020 to 62,486 hours. This difference of 41,534 burden hours is due to a reduction of burden hours expected by recalculating burden requirements for sections 21 CFR 814.82 and 21 CFR 814.84, and by implementing the FDAMA section for 30 Day Notice/135 Day PMA supplement review in a separate Final Rule. The 30-Day/135 Day review was originally instituted by FDAMA and is now covered in revisions to 21 CFR 814.39 (revised in April, 1998).**

**16. Plans for Tabulation and Publication and Project Time Schedule**

**This collection of information will not be published for statistical use.**

**17. Reason(s) Display of OMB Expiration Date is Inappropriate**

**Currently, CDRH is not requesting an exemption for display of the OMB expiration date.**

**18. Exception to Certification for Paperwork Reduction Act Submissions**

**Currently, CDRH is not requesting an exemption to Certification for the Paperwork Reduction Act Submissions.**

**19. Certification for Paperwork Reduction Act Submissions**

**B. Collection of Information Employing Statistical Methods**

**This information collection does not employ statistical methods.**

**List of Attachments to Supporting Statement**

| | |
|---|---|
| **Attachment A -** | **Code of Federal Regulations (21 CFR Part 814)** |
| **Attachment B -** | **The Federal Food, Drug, and Cosmetic Act, Section 515** |
| **Attachment C-** | **Federal Register 60 day Notice Soliciting Comments on "Premarket Approval of Medical Devices - 21 CFR 814", October 6, 1998, Docket No. 96N-0721.** |
| **Attachment D** | **CPI/Guidant March 7, 1997 "Comments to Docket Number 96N-0491"** |